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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|-------------------|
| 10/573,945 | 03/07/2007 | Philip A. Beachy | JHU1920-1 | 2047 |
| 28213 | 7590 | 03/30/2009 | EXAMINER | |
| DLA PIPER LLP (US) 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133 | | | | ROBINSON, BINTA M |
| ART UNIT | | PAPER NUMBER | | |
| 1625 | | | | |
| MAIL DATE | | DELIVERY MODE | | |
| 03/30/2009 | | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/573,945 | BEACHY ET AL. | |
| | Examiner | Art Unit | |
| | BINTA M. ROBINSON | 1625 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on ____.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 6-23 and 26-41, 45-59 is/are withdrawn from consideration.
- 5) Claim(s) ____ is/are allowed.
- 6) Claim(s) 1-5, 24, 25 and 42-44 is/are rejected.
- 7) Claim(s) ____ is/are objected to.
- 8) Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on ____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. ____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____ . | 6) <input type="checkbox"/> Other: ____ . |

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1. Detailed Action

2. The examiner notes applicant's election of Group I, drawn to claims 1-36 and applicant's selection of species of compound 2. Claims 37-59 are withdrawn from consideration as being drawn to a non-elected invention. Attorney Ed Robinson also agreed on March 20, 2009 to withdraw claims 6-23 and 26-36 from consideration as being drawn to non-elected subject matter, this non-elected subject matter being compounds not of formula I in claim 1. Claims 42, 43, and 44 are also rejoined for consideration with Group I, because they are dependent upon claim 1 and are drawn to the group I invention. This restriction is made FINAL.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 24, 25, 42, 43, 44, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor

7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

) Determining if any particular claimed compounds of formula I would be active would require synthesis of the substrate and subjecting it to testing with Applicants' screening assays and reporter gene based assays, cell-free assays. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 36-59 which merely states Applicants' intent to make and use such compounds. c) In the instant case, none of the working examples contains any of the claimed compounds of formula I. No assays are described in which any of the claimed compounds of formula I were examined and their results obtained – no data or results have been disclosed with regard to any biological or chemical assays in terms of the efficacy of the claimed compounds on the claimed diseases or on inhibiting activation of signaling pathways such as the Hedgehog pathway.

d) The nature of the invention is inhibition of signaling pathways such as the Hedgehog pathway and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the hedgehog signaling pathway, the binding activity of small ligands within this pathway, and the ability of those compounds to inhibit signaling

pathways. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician and pharmacologist would indeed question the inclusion of such diverse moieties, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (I) will all share the same biological and chemical properties. For example, R2 equal to alkoxy is not obvious and is not expected to have similar biological and chemical properties to halogen. R3 equal to nitro is not obvious over acetyl and is not expected to have similar biological and chemical properties to acetyl. The diverse claimed moieties are chemically non-equivalent and there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including

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both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree or a pharmacologist with a PhD and several years of experience. He would be unaware of how to predict *a priori* how a changing a one nonobvious moiety to another would affect biological activity. In view of the divergent moieties with varied chemical and biological properties, the skilled pharmacologist would indeed question the inclusion of all of these compounds, commensurate in scope with these claims.

g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with

chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of thousands of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various moieties, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

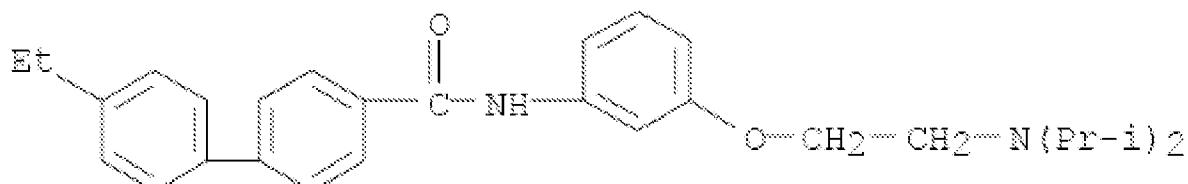
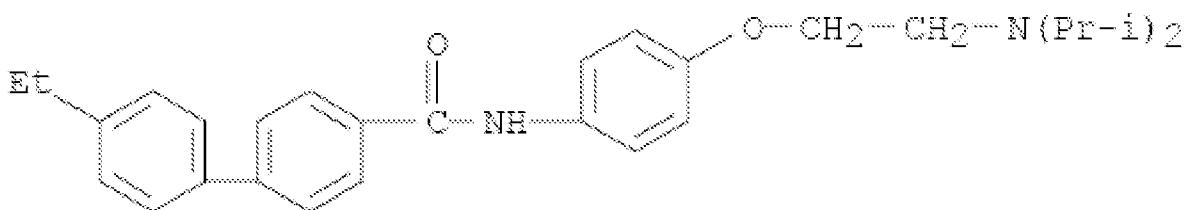
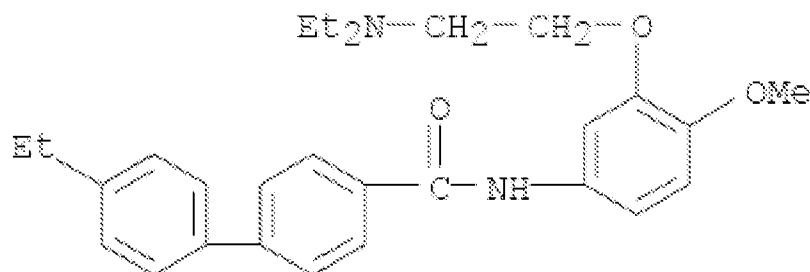
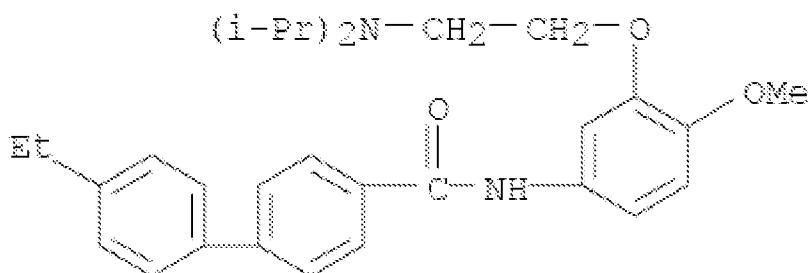
4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 24, 42, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hcaplus 1999:48617. (See Reference U) in view of Patani et. al.

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Hcaplus 1999:48617 teaches the compounds



The difference between the prior art compounds and the instantly claimed compounds is the teaching of a phenyl ring in the prior art as a replacement of the pyridyl ring in the instant compound. Patani et. al. teaches that bioisosteres are groups of compounds which elicit similar biological activity which has been attributed to common

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physicochemical properties. See page 3148 of Patani et. al. Patani et. al. also teaches that phenyl and pyridyl are bioisosteric replacements of one another that result in retention of biological activity within different series of pharmacological agents. It would have been obvious to one of ordinary skill in the art to modify the prior art compounds to structurally similar compounds which are bioisosteres of one another. Accordingly, the compounds and compositions are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the prior art compounds.

The election of species is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0670.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

/Binta M Robinson/
Examiner, Art Unit 1625

/Janet L. Andres/

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Supervisory Patent Examiner, Art Unit 1625